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Alanine Transaminase Individual Variation Is a Better Marker than Socio-Cultural Factors for Body Mass Increase in Healthy Males

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ABSTRACT

Overweight and obesity are considered a major burden on public health in developed countries. Underlying etiologies are enigmatic and metabolic causes have been suggested to various extents before. We analyze links of major blood parameters to individual body mass in a young male cohort, controlling for socio-cultural factors, in order to explore an underlying metabolic cause of obesity. Anthropometric (height, weight) physiologic (blood pressure) and metabolic data (total cholesterol, alanine transaminase, creatinine, postprandial glucose, blood cell counts, haemoglobin) of Swiss conscripts (N = 46,684; 18 - 20 yrs old; 2005-2007 census) were examined in the context of their socio-cultural groupings (occupation, mother tongue, religion) by ANOVA and stepwise multiple regression analysis. Swiss Armed Forces recruiting is mandatory, thus each year's group studied reflects more than 80% of a year's male Swiss citizen birth cohort. Individual body mass index ranged from 19 kg/m² (5th percentile) to 29 kg/m² (95th percentile) with a median of 22 kg/m². BMI increases significantly, even within its normal range (18.5 - 25 kg/m²) with increases in alanine transaminase ($r^2 = 0.10$), total cholesterol ($r^2 = 0.08$) and erythrocyte counts ($r^2 = 0.02$). All other parameters, including socio-cultural categories, explain individually 1% or less of total BMI variation. Glucose values do not correlate with BMI significantly, thus suggesting a specific metabolic co-etiology of individual mass increases. There may occur a biochemical anomaly in liver metabolism that underlies development of the metabolic syndrome later in life. Were it so, pharmacological intervention rather than just diet and exercise regime could be more effective treatment of obesity.

Keywords: Switzerland, Young Men, Conscripts, Obesity, Language

1. Introduction

Obesity is considered a major problem for public health in the 21st century. It is a major factor influencing economy not only because of correlated disease burden, but also through obesity limiting capacity of some individuals to work and by requiring changes in industrial construction standards, especially in the garment industry [1] and where ergonomic considerations are prominent.

Obesity is commonly considered to be a result of the lifestyle of overnutrition and underexercise. Based on this concept, measures aimed at limiting the increase in adiposity have failed to reverse the trend. Normal biological variation in nutritional physiology and thus in individual responses to food intake and energy expenditure is largely ignored. It can be argued that obesity has

two sets of causes: 1) purely lifestyle-related and 2) biological variations. There is natural variation among individuals in metabolic processes such as caloric requirements, energy expenditure, nutrient absorption, processing of nutrients and appetite regulation in response to the variation in neurohormonal regulation of the central nervous system. Moreover, certain metabolic anomalies, such as diabetes type I, predispose to adiposity. The prevalence of individuals with metabolic problems may be increasing as the variation in human biological characteristics is increasing under conditions of relaxed selection. This process has been documented for anatomical variations and anomalies [2-6], while with respect to metabolic variation it remains hypothetical.

Strategies of providing public with general advice on how to control body weight treat all people the same way

and due to varying levels of comprehension of messages and poor compliance with diets and exercise regimes, largely fail. It seems that targeting groups-at-risk, and giving them individual attention, may be more effective [7]. Thus, to introduce such individualized strategies, we must be able to understand what individually variable factors increase risk of obesity.

Obesity has multiple etiologies and thus any single factors can be expected to show only low correlations to adiposity in a cross-sectional study. Therefore such studies require very large samples in order to determine with confidence the significance and the magnitude of the influence of particular factors. In the present-day social environment, collection of very large samples of uniformly measured biological variables is difficult. With age, body weight naturally increases while various diseases may occur and their weight-changing effects accumulate throughout the life too. Thus, increasing sample size by including persons of various ages may confound results. This explains relative scarcity of unbiased large sample studies of biological characteristics associated with obesity.

One of possible approaches to the study of individual variation in the obesity risk is to investigate co-variation of adiposity with a number of biological characters while controlling for cultural and socioeconomic differences in a large sample of young people of the same age. Military conscription in Switzerland provides a unique opportunity for such a study. Each Swiss male upon reaching age of 19 years is required to present himself for conscription, some females can, and do, volunteer and undergo the same conscription procedures. During those procedures personal data are collected and medical examinations conducted. In the course of medical examination measurements of body weight and height are made, blood samples taken for routine analyses, and physical fitness is tested. All conscription procedures are fixed and thus provide a standard set of data. Shortcoming of limited data depth (e.g. lack of skinfold measurements) in this situation is compensated by very large sample, because all members of a particular male birth cohort must present themselves for conscription. They no longer constitute a sample from a particular cohort – they actually are an entire cohort, a statistical general population of their birth year. It is only those males who reside abroad at the time of conscription, are seriously physically disabled (e.g. not able to walk) or have some very valid special excuse that do not present themselves for conscription and related physical examination.

In this paper we explore relationships among obesity as measured by body weight and the body mass index (BMI), socioeconomic variables and a number of blood

parameters which may be indicative of metabolic processes (**Table 1**).

2. Methods and Procedures

A total of 101,392 male conscripts of all Swiss cantons were examined during draft years 2005-2007, thus reflecting 83% of all Swiss male citizens in their age cohort (Federal Statistical Office, FSO, www.statweb.admin.ch, Table BEV016A). Only 19 and 20 years olds with complete information regarding all variables of interest in this study were included in our sample to exclude possible age-related data confounding. This reduced sample size to 46,684 individuals. Swiss Armed Forces require mandatory multi-day recruitment [8], with identical qualitative standards for technical equipment and organization as defined by Swiss Armed Forces Regulations (Nosologia militaria # 59.010; Medizinische Beurteilung der Diensttauglichkeit und Dienstfähigkeit der Stellungspflichtigen und Angehörigen der Armee MBDD # 59.002). Tests are taken under professional medical supervision at seven especially dedicated conscription centers located in all major Swiss geographical regions. Self-reported professions and vocations of conscripts were grouped into categories according to the Berufsnomenklatur 2000 classification of the FSO (Agriculture, Engineering & IT, Construction & Mining, Trade, Services, Management & Administration, Health & Education, Students, Apprentices, Industrial Production) to study potential “peer-group”-effects. Occupations were grouped according to economic sector and nature of task. The sectoral aggregation (agriculture, industrial production, engineering & IT, construction & mining, trade services, management and administration, health & education) is based on the Swiss Standard Classification of Occupations 2000 (SSCO 2000) published by the Swiss Federal Statistical Office (www.bfs.admin.ch). The classification of occupation by nature of task (legislators, senior officials and managers; professionals; technicians and associate professionals; clerks; service workers and shop and market sales workers; skilled agricultural and fishery workers; craft and related trades workers; plant and machine operators and assemblers; elementary occupations) follows the International Standard Classification of Occupations (ISCO-88) of the International Labour Organization (www.ilo.org).

Since the conscripts in the data set are 19 or 20 years old, we add two categories for students and apprentices. Distributions are shown in **Figures 1(a)-(b)**.

Main language in the individual’s municipality and religion in their districts of residence were used to capture cultural influences. All sectors of economy, social status categories, main languages and religions of Switzerland

Table 1. Descriptive statistics of biological variables used.

Variable	N	Mean	Median	Stdev	5%	95%
Height (cm)	46,684	178.2	178.0	6.4	168.0	189.0
Weight (kg)	46,684	73.0	71.0	11.8	57.6	95.0
BMI (kg/m ²)	46,684	23.0	22.0	3.4	19.0	29.0
BPsystolic (mm Hg)	45,293	132.6	134.0	11.2	114.0	151.0
BPdiastolic (mm Hg)	45,292	77.3	78.0	8.3	63.0	90.0
Cholesterol (mmol/l)	46,684	4.1	4.0	0.8	3.0	5.4
Creatinine (mmol/l)	46,684	80.0	78.0	12.9	62.0	103.0
ALT (μm/l)	46,685	26.3	22.0	17.0	13.0	51.0
Glucose (mmol/l)	46,186	4.8	4.8	0.8	3.5	6.2
Thrombocytes (× 1000/μl)	46,492	260.3	256.0	53.2	182.0	352
Leukocytes (× 1000/μl)	46,491	7.3	7.1	1.8	4.9	10.6
Neutrophils (× 1000/μl)	46,321	4.5	4.2	1.6	2.5	7.5
Lymphocytes (× 1000/μl)	46,321	2.1	2.1	0.6	1.3	3.2
Monocytes (× 1000/μl)	46,321	0.49	0.47	0.16	0.28	0.78
Eosinophiles (× 1000/μl)	46,321	0.16	0.12	0.14	0.03	0.40
Basophiles (× 1000/μl)	46,321	0.04	0.04	0.02	0.00	0.08
Erythrocytes (× 1,000,000/μl)	46,491	5.2	5.2	0.3	4.7	5.7
Haemoglobin (g/l)	46,492	157.3	157.0	8.9	143.0	172.0

are represented among our conscripts **Figures 1(c)-(d)**.

Laboratory assessment includes blood sample and urine analysis [9]. Individual total cholesterol, creatinine, alanine transaminase, postprandial serum glucose level, erythrocyte count, leukocyte count and hemoglobine were examined. All individual data were made fully anonymous before analysis; no additional ethical approval is required for fully anonymized Swiss governmental statistical data (Swiss data privacy act, SR 235.1; 19.6.1992).

Statistical analysis (using Excel[®] SPSS11 and Matlab[®], version 7.6.0324 [R2008a]; The MathWorks GmbH, Aachen, Germany) was performed by means of multivariate analysis of variance and stepwise multiple regression analysis after logarithmic transformation of those continuous variables which had skewed distributions.

3. Results

Our sample shows parameters of distributions of studied variables characteristic for young healthy males (**Table 1**). Among 46,684 conscripts 1796 (3.8%) are underweight (BMI < 18.5 kg/m²), 33,422 (71.6%) are of nor-

mal body mass, 9264 (19.8%) are overweight (BMI > 25 but < 30 kg/m²) and 2202 (4.7%) are obese.

Analysis of variance in the entire material indicates that the variable having the greatest contribution to the total variance of body mass is the level of alanine transaminase (ALT also called GPT—glutamic pyruvic transaminase) followed by systolic blood pressure and cholesterol. Other variables, including sociocultural ones, contribute each just around 1% or less to the total variance (**Table 2**).

Stepwise multiple regression analysis confirmed those results showing that in the entire cohort nearly 20% of variance is jointly explained by the levels of ALT and cholesterol while systolic blood pressure adds some 3.5%. Systolic blood pressure correlates with BMI independent of the levels of ALT and cholesterol.

When socioeconomic variables and blood pressure are kept constant in partial correlation coefficients calculations (**Table 3**) ALT shows the highest correlation with BMI followed by cholesterol level and erythrocyte count. Surprisingly, cultural and socioeconomic factors contribute little to the variance in the BMI—just about 1% - 2%

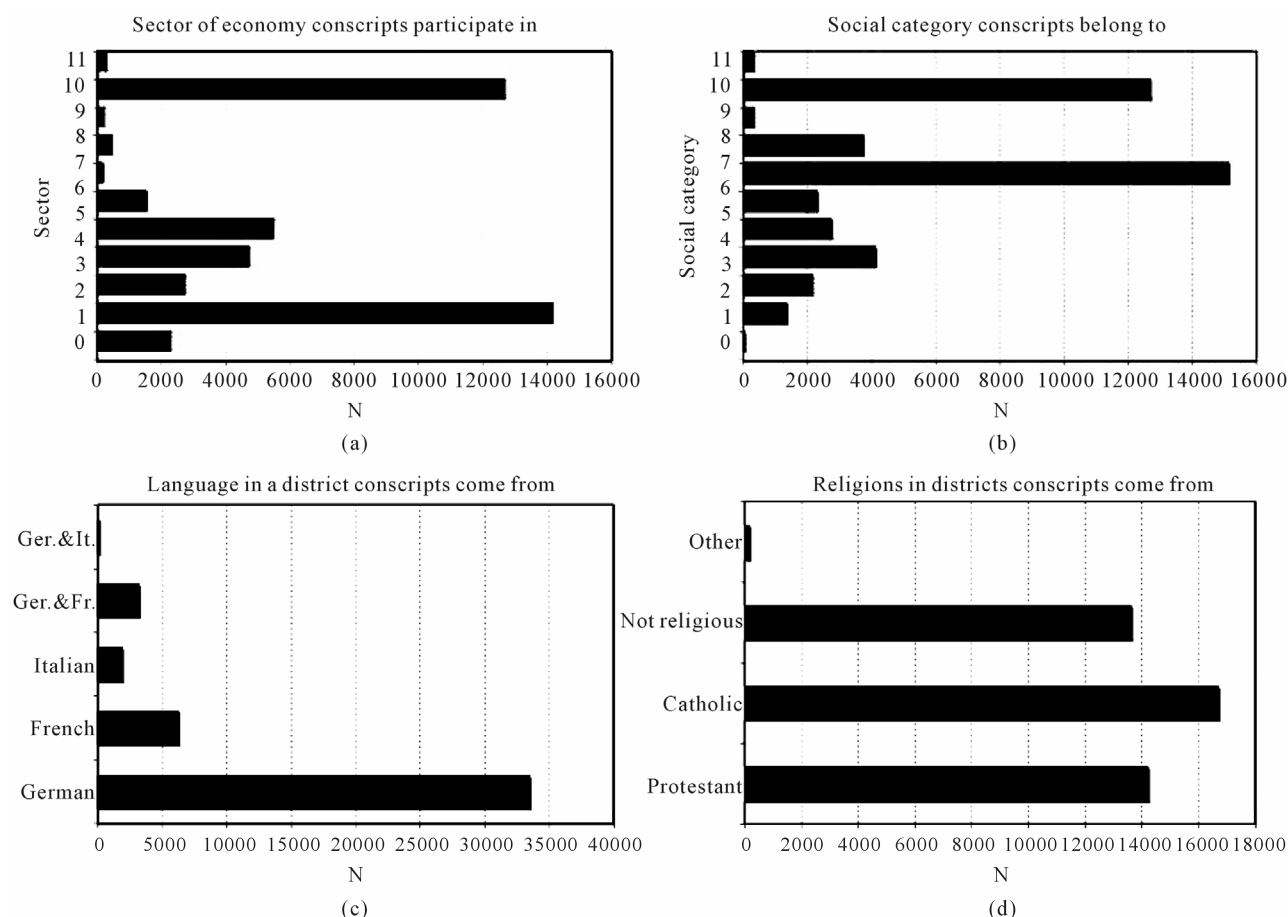


Figure 1. Distribution of categorical socio-cultural variables in the entire sample of conscripts. (a) Sector of economy conscripts participate in (classified after SSCO 2000): 1 - agriculture, 2 - industrial production, 3 - engineering and IT, 4 - construction and mining, 5 - trade, 6 - services, 7 - management and administration, 8 - health and education, 9 - missing, 10 - university/high school students, 11 - apprentices; (b) socioeconomic categories conscripts belong to (classified after ISCO 88) 1 - legislators, senior officials and managers, 2 - professionals, 3 - technicians and associate professionals, 4 - clerks, 5 - service workers and shop and market sales workers, 6 - skilled agricultural and fishery workers, 7 - craft and related trades workers, 8 - plant and machine operators and assemblers, 9 - elementary occupations, 10 and 11 like in (a); (c) languages in the conscripts' district. Note: there are no districts with mixture of French and Italian; (d) religious affiliations in conscript's districts. "Other" includes mostly Protestant-Catholic mixed religions.

though their contributions are formally significant (**Tables 2** and **4**). When their influence is practically completely removed by "experimental" selection of groups homogenous with respect to language and occupation – German speaking university students and German speaking low-skilled workers—the pattern of contribution of biological variables within such groups remains the same with the greatest contribution of ALT and much lesser contribution of cholesterol (**Table 5**).

The pattern of the contribution of the variables – greatest of those reflecting liver function, small of socio-cultural factors, remains the same in groups of individuals with normal (18.5 - 24.9), overweight (25.0 - 29.9) and obese (>30) BMI values (all in kg/m²) (**Figure 2**). In

underweight individuals (BMI < 18.5 kg/m²) no relationships were found at all. Also, very obese individuals (BMI > 35 kg/m²) seem to have no relationship between BMI and ALT (**Figure 2**, end of the regression line).

To confirm these findings further we have selected only those individuals who were healthy according to the following criteria: BMI 18.5 - 24.9 kg/m², cholesterol below 5 mmol/l, glucose below 7.8 mmol/l, ALT below 23 µmol/l and systolic blood pressure below 130 mmHg. In this artificially created "healthy" group ALT still had the greatest, significant relationship with BMI (**Table 6**). Finally, it is interesting to note that postprandial levels of glucose (**Table 2**) do not co-vary with BMI at all in any group.

Table 2. Results of ANOVA and Stepwise Multiple Regression linking BMI to all variables studied. N = 44,553.

ANOVA variables ^a	Sum of squares	Prob > F
ALT	39112.3	0.000
Cholesterol	10760.5	0.000
Systolic blood pressure	9774.1	0.000
Erythrocytes	1372.7	0.000
Creatinine	1078.7	0.000
Sector (Figure 1(a))	964.1	0.000
Social status (Figure 1(b))	428.4	0.000
Glucose	367.9	0.000
Basophiles	333.7	0.000
Language	258.3	0.000
Diastolic blood pressure	222.9	0.000
Error	385202	
Total	501969.6	N = 44553
Stepwise multiple regression variables ^b	Cumulative R ²	Sign. F
ALT	0.138	0.000
ALT & BPsyst	0.178	0.000
ALT, BPsyst & Cholest	0.206	0.000
ALT, BPsyst, Cholest & SES	0.214	0.000

^aAll variables with significant F values are included. Note: small sums of squares for social variables and for glucose; ^bInclusion of variables into the regression was limited to those contributing more than 0.5% of the explanation of the total variance in BMI.

The greatest portion of the total variance in our analyses is the unexplained variance. Measurement error of BMI is rather small (about 5% [10]) but physiological parameters may have larger measurement error variances as indicated by about 30% - 40% errors assessed for blood pressure, cholesterol and glucose concentration by Whitlock *et al.* [10]. This seems unavoidable in a cross sectional-study where short-term individual variations cannot be controlled for. Were these errors controlled for, our findings would be stronger.

4. Discussion

Surprisingly, we have found very little influence of socio-economic and cultural factors on the variance of BMI in the cohort of young Swiss males. Furthermore, biological variables related to characteristics of blood cells, kidney function, and postprandial glucose levels did not display any substantial contribution to the BMI variance. In the case of glucose levels, our results may not necessarily reflect natural metabolism of some individuals, especially those with diagnosed diabetes who are already on medication.

It was only liver function indicators that influenced strongly variation in BMI. Both ALT and cholesterol, the two variables showing the greatest contributions to the total BMI variance, are related to the liver function including links to metabolic pathways of gluconeogenesis and glycolysis and thus to the energy processing in the body. Blood pressure correlation with BMI seems to be a

Table 3. Partial correlation coefficients^a among biological variables when socioeconomic variables and blood pressure are kept constant. N = 44,547.

Variable	BMI	ALT	Cholesterin	Creatinine	Glucose	Thromboc	Leukocytes	Neutrophil	Lymphocyt	Monocytes	Eosinophil	Basophiles	Erythrocytes	Hemoglobin
BMI	1.00	0.35	0.25	0.07	0.05	0.04	0.09	0.04	0.12	0.07	0.05	0.02	0.13	0.10
ALT		1.00	0.22	0.03	0.05	0.04	0.06	0.02	0.10	0.05	0.03	0.03	0.11	0.11
Cholesterol			1.00	0.06	0.08	0.09	0.05	0.03	0.09	-0.01	-0.01	0.05	0.16	0.19
Creatinin				1.00	0.01	-0.05	0.07	0.06	0.06	-0.02		-0.04	0.04	0.05
Glucose					1.00	0.02	0.08	0.12	-0.03	-0.07	-0.08	0.01	-0.02	-0.01
Thrombocyt						1.00	0.25	0.19	0.18	0.14	0.06	0.17	0.01	-0.05
Leukocytes							1.00	0.93	0.37	0.51	0.13	0.28	0.11	0.11
Neutrophil.								1.00	0.02	0.39	-0.03	0.17	0.11	0.12
Lymphocyt.									1.00	0.22	0.22	0.28	0.02	-0.01
Monocytes										1.00	0.14	0.17	0.05	0.06
Eosinophil.											1.00	0.18		-0.02
Basophiles												1.00	0.07	0.08
Erythrocytes													1.00	0.68
Hemoglobin														1.00

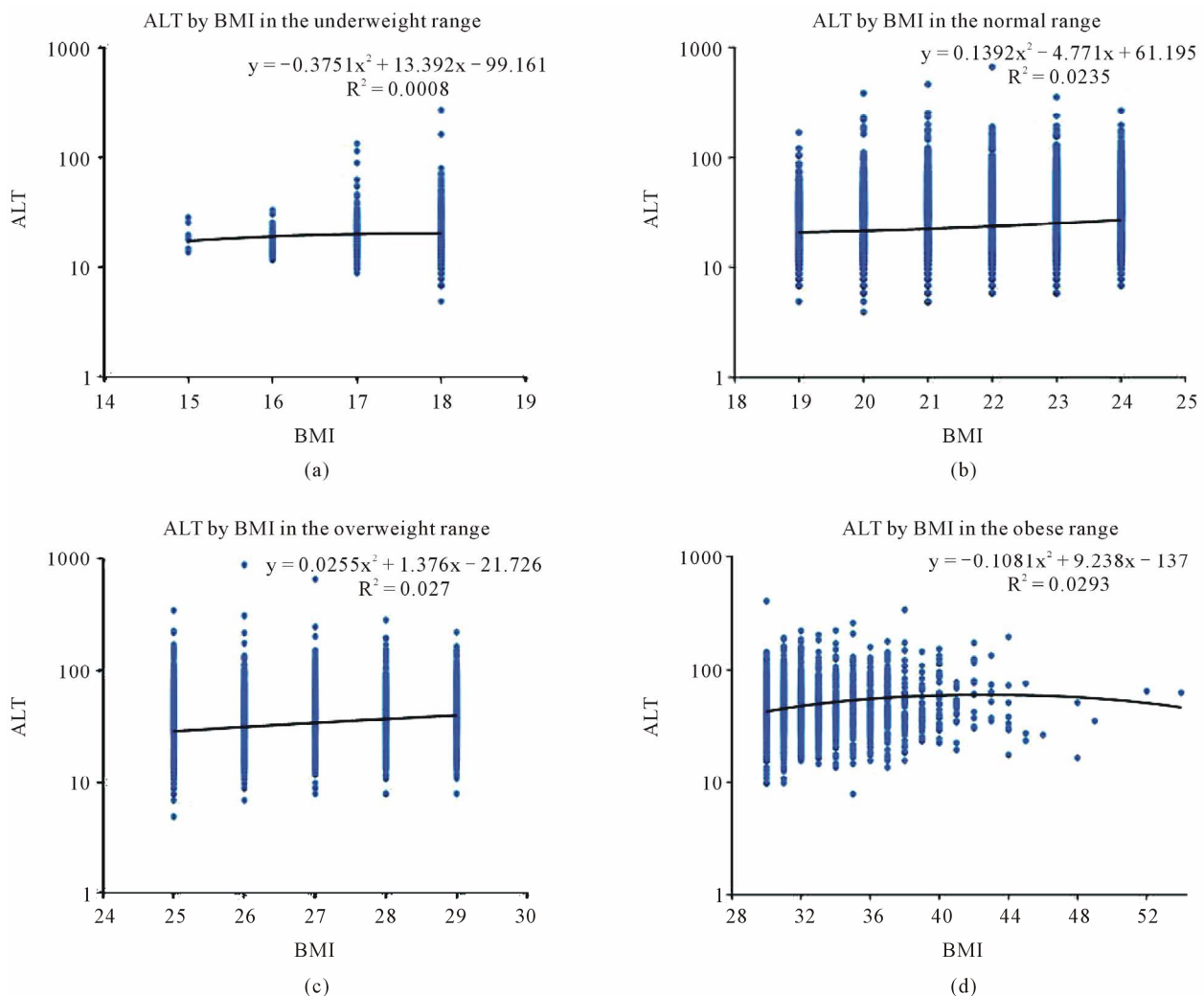


Figure 2. Second order polynomial regressions of ALT GPT on BMI. From among all models fitted by SPSS the second order regression produced the best fit. (a) Underweight conscripts. Note that the slope of the squared component is negative while R squared is very low; (b) conscripts with normal body mass. Slope of squared component is positive and R squared very significant ($p < 0.001$); (c) overweight conscripts. Slope is positive, R squared highly significant ($p < 0.001$); (d) obese conscripts. Note negative slope of the squared component producing downward direction of the line among very obese conscripts (BMI > 35 kg/m²).

simple result of increased body mass.

Switzerland is a highly developed country with egalitarian political system. Thus, all Swiss citizens, irrespective of their mother tongue and socio-economic situation, grow and live in conditions very close to the optimum for biological development. With the lack of variation in living conditions, biological characteristics come to the fore as determinants of obesity.

Parameters of liver function such as ALT and cholesterol levels have long been known to correlate with the metabolic syndrome and thus with BMI [11-13]. It has not been clarified, however, whether this correlation is a result of adiposity causing increase in ALT levels, or

vice versa. Although there is no doubt that in excessively obese patients serious liver malfunction occurs [14], producing elevated levels of ALT and cholesterol, there are many individuals of normal body mass [15], or only mildly overweight [16] who have elevated levels of ALT. Our study cohort, comprising only young males, who at the time of conscription were apparently healthy, shows persistent correlation of ALT levels with BMI irrespective of actual body mass even in the “normal” BMI range. This is even true amongst a sample selected on all available parameters as absolutely “healthy”. Our study design is cross-sectional and thus we cannot directly show a causal relationship between ALT and increased body

Table 4. Results of ANOVA and Stepwise Multiple Regression linking BMI to socioeconomic and cultural variables studied. N = 46,673.

ANOVA variables	Sum of squares ^a	Prob > F
Sector	1174.1	0.000
Social	676.3	0.000
Language	145.7	0.011
Religion	96.9	0.033
Error	494458.5	
Total	501969.6	N = 44553
Stepwise multiple regression variables	cumulative R ²	Sign. F
Social category	0.010	0.000
Economic sector	0.011	0.000

^aNote small sums of squares and small portion of total variance explained (compare Table 2). All variables making statistically significant contributions are shown.

mass, but the sample size and the fact that the relationship is ubiquitous irrespective of actual body mass range, argue for the causal relationship that deserves to be studied further.

We also selected individuals on the following criteria: systolic blood pressure below 120 mmHg, cholesterol level below 5.0 mmol/l, glucose concentration below 7.8 mmol/l, thrombocytes below 260,000/ μ l and leucocytes below 7100/ μ l. Such selection removes all risk factors of metabolic syndrome, as defined by the American Heart Association [17] and the Mayo Clinic [18], except BMI. In a group so selected, ALT levels still contribute significantly to body mass (Table 7).

A relationship between ALT and BMI was observed amongst professional athletes before [19]. In a Japanese sample, non-alcoholic, non-overweight participants of both sexes had a significant relationship of fatty liver resulting in high ALT levels and body fat [15]. These findings indicate that variation in liver function in normal individuals influences variation of body mass. In populations average liver function worsens with age [14] and

Table 5. Results of ANOVA and Stepwise Multiple Regression linking BMI to biological variables in German speaking conscripts divided into "Social" (socioeconomic status) groups. In ANOVA only the four variables with greatest sums of squares are included. Inclusion of variables into the regression was limited to those contributing more than 0.5% of the explanation of the total variance in BMI.

Group	ANOVA variables	Sum of squares	Prob > F
German-speaking	ALT	16355.3	0.000
Low SES ("Social" > 6)	Cholesterol	4019.0	0.000
N = 15,699	Erythrocytes	612.9	0.000
	Creatinine	339.3	0.000
	Total	187838.2	
German-speaking	ALT	5317.9	0.000
High SES ("Social" 1 + 2)	Cholesterol	2288.7	0.000
N = 8,642	Creatinine	400.5	0.000
	Erythrocytes	189.0	0.000
	Total	81135.6	
Group	Stepwise multiple regression variables	cumulative R ²	Sign. F
German-speaking	ALT	0.151	0.000
	ALT & Cholesterol	0.183	0.000
Low SES ("Social" > 6)	ALT, Cholesterol & Lymphocytes	0.188	0.000
	ALT, Cholesterol, Lymphocytes & Erythrocytes	0.194	0.000
German-speaking	ALT	0.119	0.000
	ALT & Cholesterol	0.157	0.000
High SES ("Social" 1 + 2)	ALT, Cholesterol & Creatinine	0.163	0.000
	ALT, Cholesterol, Creatinine & Erythrocytes	0.169	0.000

Table 6. Results of ANOVA and Stepwise Multiple Regression linking BMI to biological variables in a “Healthy” group (normal BMI, normal cholesterol, normal ALT, normal blood pressure). All variables with significant F included into ANOVA results. Inclusion of variables into the regression was limited to those contributing more than 0.5% of the explanation of the total variance in BMI. N = 6549.

ANOVA variables	Sum of squares	Prob > F
ALT	116.0	0.000
Cholesterol	53.6	0.000
Systolic blood pressure	50.0	0.000
Creatinine	30.5	0.000
Erythrocytes	9.3	0.036
Error	13777.5	
Total	14169.9	N = 6528
Stepwise multiple regression variables	Cumulative R ²	Sign. F
ALT	0.011	0.000
ALT & Cholesterol	0.016	0.000

Table 7. Results of ANOVA and Stepwise Multiple Regression linking BMI to biological variables in a group without any signs of “metabolic syndrome” except full BMI range. All significant contributions to total variance are included. Inclusion of variables into the regression was limited to those contributing more than 0.5% of the explanation of the total variance in BMI. N = 1337.

ANOVA variables	Sum of squares	Prob > F
ALT	305.7	0.000
Erythrocytes	59.0	0.001
Cholesterol	57.5	0.002
Glucose	48.1	0.004
Creatinine	34.9	0.014
Diastolic blood pressure	30.0	0.023
Total	8455.2	N = 1337
Stepwise multiple regression variables	cumulative R ²	Sign. F
ALT	0.046	0.000
ALT & Erythrocytes	0.065	0.000
ALT, Erythrocytes & Creatinine	0.070	0.005

average BMI increases.

Identification of individual levels of relevant liver

functions may be used to pinpoint those young patients that are at risk of developing obesity and, thus, design for them personal coping strategies to prevent development of metabolic syndrome. Present-day treatment of potential or actual metabolic-syndrome-related obesity, by strict dietary and exercise regimes, however to a certain degree effective, requires high levels of patient compliance which are difficult to observe persistently and thus often ineffective. Our results suggest that weight gain by some individuals may be a result of their biochemical anomalies, not of gluttonous life style. Were it so, it would be possible to develop pharmacological ways of correcting liver metabolism to avoid development of obesity by a substantial portion of a population.

The fact that the greatest portion of individual BMI variance remains unexplained in our study probably has two sources: 1) measurement error and 2) individual variation in factors that were not captured by variables used in this study. These errors result primarily from diurnal and other periodic fluctuations in body functioning rather than from laboratory techniques. Undoubtedly there is individual variation in biological and socio-psychological factors underlying variation in BMI that was not captured by analysis of parameters available for this study and which shall be explored further in the future. Also, a further study including larger number of variables characterizing metabolism in more detail in participants of both sexes would be useful.

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